UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/043,665	10/05/98	RUSSELL S	MEWB112010

HM12/0919

KATHLEEN M. WILLIAMS, PHD.
PALMER & DODGE, LLP
ONE BEACON STREET
BOSTON MA 02108

EXAMINER	
SHUKLA,R	
ART UNIT	**PAPER NUMBER**
1632	17

DATE MAILED: 09/19/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/043,665	Russell et al
Examiner	**Group Art Unit**
Ram Shukla	1632

☒ Responsive to communication(s) filed on *Jul 6, 2000*

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-21* is/are pending in the applicat

Of the above, claim(s) *13-21* is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-12* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Amendment filed 07-06-2000 (paper # 15) has been entered. Amended claims 1 and 4 have been amended.

2. Claims 1-12 are under consideration in the instant application.

Claim Rejections - 35 U.S.C. § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 10-12 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition of cells made by claim 1 that would have a nucleic acid encoding a polypeptide for treating a disease or disorder, does not reasonably provide enablement for a method for treatment of a patient by administering to the patient effective amount of these cells, for reasons of record set forth in the previous office action of 1-6-00 (paper # 13). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to making and practicing the invention commensurate in scope with these claims.

Response to Applicants' Arguments:

Applicants' arguments have been carefully considered, however they are not deemed persuasive. Applicants have stated that quiescent cells transformed with claimed retroviral packaging cell line or retroviral particles are more likely to be transformed, however, these arguments are not persuasive because any cell, not just the quiescent cells, that have the receptor for the growth factor expressed by the packaging cells would be transformed. In fact, claimed method as recited (line 3 of claim 1) encompasses all the cells or any cells.

Applicants' arguments regarding the transplantation of autologous, allogeneic or xenogeneic cells are not persuasive because the art of cell transplantation is unpredictable and the specification does not provide sufficient guidance for enabling the claimed method, at the time of claimed invention was made (see the introduction section in Kohn et al). In response to applicants argument that the claimed method is not directed to the effect of growth factor on a transformed quiescent cell and therefore, the specification is not required to enable the effect of growth factor in a quiescent cell, it is noted that effect of the growth factor on the quiescent cells is the crucial step that would induce the quiescent to divide. Therefore, the effect of growth factor on the quiescent cell is important. For example, in vivo, if the growth factor displayed on the packaging cells does not induce a quiescent cell to divide, it is not clear how will the claimed method work.

Applicants have further argued that they are not required to disclose a sufficient level of all proteins that can be produced. Again these arguments are not deemed persuasive because unless there is evidence that the claimed method results in transformation of quiescent cells in vivo by the retroviral proteins and that there is a production of the targeted therapeutic protein which produces a therapeutic effect, how then can a pharmaceutical composition be enabled for its recited use. Additionally, it is not clear how then can a pharmaceutical composition can be enabled if there is no evidence that the pharmaceutical composition exists in vivo in a cell to be treated and that it has therapeutic effect. It is noted that the specification has not provided any evidence whether quiescent cells in vivo would be transformed by the claimed method in vivo, and in view of the unpredictability of the method, prophetic examples and disclosures would not be sufficient for an artisan to practice the claimed method without undue experimentation.

Applicants have also argued that the specification teaches how to produce a cell that expresses an art accepted level of a protein that is known to be useful for disease. In response it is noted that when there is no evidence that the claimed method works in vivo and produces art accepted levels of a protein in vivo and the state of the art is unpredictable. Therefore, it is not clear how can the results seen in art accepted method be used to support the enablement of the claimed method and how can general statements made in the specification such as quoted in the Applicants' response (page 6, last paragraph) support enablement of the claimed methods.

In conclusion, the specification does not provide sufficient guidance as to how an artisan of skill would have dealt with the art recognized problems and specific issues mentioned above regarding the claimed method, without undue experimentation. Therefore, as noted in the previous office action, while the specification is enabling for making a cell composition that has been transduced with a retroviral particle that expresses a fusion protein of a growth factor and envelope, it is not enabling for a method of treating a patient using said cells.

Claim Rejections - 35 U.S.C. § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

6. Claims 1,2, 4-5, and 7- 9 are rejected under 35 U.S.C. 102(e) as being anticipated by Ralph et al, as noted in the previous office action (paper # 13).

Response to Applicants' Arguments:

Applicants arguments have been carefully considered, however they are not deemed persuasive. Regarding applicants argument that the Paul et al do not teach retroviral packaging cells bearing chimeric targeting proteins on their surface, applicants are directed to column 11, lines 43-67 and lines 1-9 of column 12, particularly lines 5-9, wherein Paul et al teach packaging cell lines that express the chimeric proteins. Regarding the issue of the expression of the growth factor on the surface of the packaging cell line, it is noted that if a growth factor used in the chimeric protein is membrane associated and contains an extracellular domain, it would be expressed on the surface of the cell it is introduced in. Paul et al list growth factors in lines 45-67 in column 9 continued in lines 1-19 in column 10) and this list includes cytokines and growth factors that interact with receptors on totipotent hematopoietic stem cells, such as flk-2 receptor.

Regarding the argument that claim 1 recites a method of transforming a population of quiescent cells, it is noted that the Lymphohematopoietic cells will inherently comprise quiescent cells and there is nothing in the claimed method or in the specification which indicates that the claimed method would only transform quiescent cells, not any other cell. Applicants have further argued that the art shows that not all hematopoietic cells are quiescent cells. However, this does not matter because the method of Paul et al should be able to transduce the quiescent cells in a population of cells. Paul et al teach, "This will be generally advantageous in the context of gene delivery since it can be used to promote proliferation and thus the transformation of the targeted cell in a given cell population" (see lines 25-29, column 15 in US 5,736,387). Additionally, Applicants argument that hematopoietic stem cell is not synonymous with the term quiescent is not deemed persuasive because hematopoietic stem cells would inherently comprise quiescent cells as indicated by claim 2.

Claim Rejections - 35 U.S.C. § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over Paul et al in view of Lyman et al for reasons of record set forth in the previous office action (paper #13).

Response to Applicants' Arguments:

Applicants' arguments have been carefully considered, however they are not deemed persuasive. Applications have stated that Lyman et al do not teach quiescent hematopoietic stem cells and that this art does not teach retroviral packaging cell line and even if the references were combined they do not provide the invention as claimed. Regarding the issue of transforming quiescent cells and retroviral packaging cell line expressing a growth factor, Applicants are directed to the response to Applicants arguments in paragraph 6 above and it is reiterated that Paul et al teach the cells while Lyman et al teach the growth factor (flt3) and that by combining the teachings of the two cited prior arts, claimed method can be practiced with

reasonable expectation, as has been noted in the previous office action (paper # 13). Applicants have not provided any specific arguments as to why it would not have been obvious to combine the teachings of Paul et al and Lyman et al to make the claimed invention of claim 3, as noted in the previous office action.

9. Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ralph et al, Lyman et al as applied to claims 1-5 and 7-9 above, and further in view of Beutler et al for reasons of record set forth in the previous office action (paper # 13).

Response to Applicants' Arguments:

Applicants' arguments have been carefully considered, however they are not deemed persuasive. Applicants have argued that Beutler et al do not teach a retroviral packaging cell line as claimed for transforming quiescent cells. Applicants have also argued that Beutler et al teach cleavage of the protein after it is secreted into the cellular supernatant and Beutler et al do not teach or suggest intracellular cleavage of a chimeric protein. In response it is noted that there is no such limitation in the claim that the chimeric protein is cleaved intracellularly. Even if the limitation was in the claim, the specification does not disclose that the cleavage takes place intracellularly. The specification discloses that the growth factor can be cleaved from the viral particle by addition of a cleaving agent, typically once the quiescent cells start dividing. The specification further discloses that the growth factor can be cleaved from the surface of the retroviral particles (see lines 21-37 in page 6 of the specification). It is not clear how can the cleavage take place intracellularly, when during infection by a retrovirus only genomic RNA and associated proteins are introduced in the infected cell, not the proteins expressed on the cell surface. Regarding the argument that there is no reason to expect that the addition of a cleavage agent to a cell would not interfere with the normal physiology of the cell, it is noted that the specification as filed has disclosed to use factor X and Beutler et al also disclose that thrombin cleavage site or factor X cleavage site can be used. If factor X does not affect cellular physiology in the case of the claimed method, why would it affect in Beutler's method. Furthermore, the claim is not limited to a method wherein the protease works intracellularly and it does not affect the physiology of a cell to be transformed or a cell that is transformed. Regarding the issue of motivation, it is noted that it would be obvious to an artisan that the use of the growth factor is

only for the purpose of cell activation and once cell is activated, therefore, it would be logical and obvious to get rid of the growth factor after a cell is activated.

Applicants have again argued that the combined references do not teach transformation of quiescent cells or a retroviral packaging cell line as claimed and again Applicants are again directed to the response set forth in paragraph 6. As has been noted in paragraph 6 above, the quiescent cells are inherently comprised in hematopoietic cells and Paul et al teach retroviral packaging cells expressing nucleic acid encoding a growth factor. According, it would have been obvious for an artisan to combine the references of Paul et al, Lyman et al and Beutler et al and make the claimed invention with reasonable expectation of success, as noted in the previous office action (paper # 13).

Therefore, the claimed inventions would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made in the absence of evidence to the contrary.

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner can normally be reached on Monday through Friday from 7:30 a.m. to 4:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached on (703) 305-6608. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 305-0196.

Ram R. Shukla, Ph.D.

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER